January 23, 2006
US Serial No. 09/816,289

REMARKS

Claims 2 and 9 - 26 are cancelled hereby as drawn to a non-elected invention, but may be presented in a divisional application. Claims 1 and 3 – 8 are currently under examination in this application.

The rejection of claims 1 and 3 – 8 under 35 USC 112, first paragraph, for nonenablement was maintained. This rejection is again respectfully traversed.

Applicants' arguments/remarks appearing in the previous response to this rejection are incorporated into this response. In reply to the additional comments made in italics at pages 6 – 8 of the instant Office Action, Applicants submit the following.

It appears there is some misunderstanding about the mechanism of a chronic "carrier" state. With *C. diphtheria*, and *P. aeroginosa*, the clinical manifestations of disease are the result of the toxin (e.g., EF-2 in diphtheria). For whatever reason, in a carrier state with pathogenic organisms (i.e., those organisms having the ability to produce the toxin – in *C. diphtheria* as a result of beta-bacteriophage lysogeny), there are no observed clinical symptoms; the chronic carriers are asymptomatic. This is well known. See, for example, the attached paper, "Guidelines for the control of Diphtheria in Canada", particularly the third paragraph on the first page. Subjects carrying the toxigenic strains have circulating antibodies to the toxin (see attached Abstract of Kostukova et al. (1977)). Thus, in the 'asymptomatic' carrier state, the toxin is immunologically kept in check.

The gist of the present invention is thus the well-reasoned discovery that when a carrier of such organisms manifests a decline in the immunological surveillance of the toxin, the toxin can begin to exert its effects in a manner

relative to the immune decline. It's somewhat irrelevant how or why this immune decline happens, just that it does. For instance, as agreed, immunity declines with age, but can also decline for a number of other reasons. For instance, Alzheimer's is observed relatively early in subjects with Down Syndrome, and these patients also manifest symptoms of aging earlier than 'normal' subjects. As stated in the specification (paragraph 0019 of the printed application), the carrier state is kept in check "until an age- or immune-disease-related decline". The premise is that, for whatever reason, a decline in immune surveillance is the culprit behind starting to see the effects of the toxin in the neuronal tissue, because the antibodies to the toxin are declining.

It is emphasized that what is taking place is a decline, not necessarily an abrupt absence of antibody to the toxin. Thus, one would not expect to suddenly see acute clinical disease; such would go against the entire theory behind the invention.

Having stated the above, the comment in the Office Action at page 6, last 3 lines, ("*Impaired immune function in the elderly runs counter to the enablement of the prophetic invention, absence any evidence to the contrary.*") is not understood; this is exactly what is disclosed in the specification – that *declining* immune function in the aged allows the toxin to act.

In the first paragraph on page 7 of the Office Action, it is stated that since Applicants don't rely on the McLay reference for support of the enablement of the disclosure, that the specification does not support the operability of the claimed invention. Applicants respectfully disagree. The McLay reference indeed is not needed to 'support' the enablement of the present invention. This reference was cited to provide anecdotal support for the theory behind the invention, not to support the invention itself.

The next paragraph on page 7 of the Office Action states that there is no support in the specification for Applicants assertion in the specification that "there is a chronic carrier state for *C. diphtheria*, which reside in the nose and throat possibly as nonpathogenic organisms or weakened pathogenic organisms." Applicants respectfully disagree; this is a well known fact, as evidence for instance in the attached Canadian paper. Thus, it is not clear why this assertion would in any way render the invention nonenabled by the disclosure.

In the third paragraph on page 7 of the Office Action, it is asserted that there is "a total lack of any basis for enablement that younger AD patients are immune impaired." As mentioned above in this response, whether immune decline is age-related or not is not relevant; it is only relevant that there is an immune decline. The specification states, as quoted above, that decline can be on the basis of age or immune disease related. Further, in paragraph 0020 of the published application, it is clearly stated that toxins secreted by pre-existing infections will begin to exert their effects on neuronal tissue "when the body's immune system is no longer capable of effectively neutralizing such toxins." Thus, the specification does not make it a condition that the immune decline has to be age-dependent. That such is the case with aging individuals, and that's the population most affected by Alzheimer's, is just a further observation in support of the invention – but it is not a necessary factor.

Regarding the comments in the paragraph bridging pages 7 and 8 of the Office Action, it is not understood why this is a point of contending that the present invention is not supported by the Johnson paper. As stated in the specification and Applicants' previous response, the observations noted in the Johnson paper do not necessarily support nor do they refute the present invention. It appears to be the position in the Office Action that Johnson actually refutes the present invention, because they noted hyperphosphorylation EF-2 in Alzheimer's brain tissue was the cause of its migration shift in 2-D gels.

Applicants emphatically state again, that even though hyperphosphorylation was observed in the work of Johnson, *this does not rule out the presence in these tissues of ADP-ribosylated EF-2.* The Office Action fails to state why it would not be possible that any other modification of EF-2 would be present in such samples. ADP-ribosylation would also result in migration shifts; there is simply no evidence in Johnson that such a modification *did not* occur. Therefore, the work disclosed in this reference does not refute the present invention. In fact, subtle amounts of ADP-ribosylation may well have occurred, which in itself would lead to the hyperphosphorylation. This is what was meant by the passage in the specification at paragraph 0015 of the published application.

Accordingly, Applicants submit that the specification provides sound scientific reasoning to support the enablement of the claimed invention. Carrier states of infection are known, for which the toxin is kept in check by an adequately functioning immune system. If the immune system declines, the toxin, which preferentially affects nerve cells, is allowed to exert its effects whereby the cells eventually die. A (booster) vaccination with the toxoid serves to boost the immune function toward the toxin, whereby cell death, and the associated clinical signs, is ameliorated. Nothing in the rejection adequately refutes this reasoning.

Accordingly, reconsideration and withdrawal of this rejection are deemed proper. The application has a presumption of patentability unless the patent office establishes a *prima facie* case of unpatentability, which has not been done in this instance.

A Petition for (two months) Extension of Time accompanies this paper. In addition, a Notice of Appeal is submitted.

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The Examiner is invited to contact the undersigned at the number or email listed below should he believe there are any remaining issues that could be more easily resolved by direct communication.

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Enclosures:

Paper entitled "Guidelines for the Control of Diphtheria in Canada", Public Health Agency of Canada, Volume 24S3 (July 1998).

PubMed Abstract of Kostyukova et al., "Pathogenesis of diphtheria carrier state from the immunological point of view", J. Hyg. Epidemiol. Microbiol. Immunol., Vol. 21:454-459 (1977).

Revocation and New Power of Attorney
Petition for Extension of Time
Notice of Appeal